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136 7590 05/27/2010 JACOBSON HOLMAN PLLC 400 SEVENTH STREET N.W. SUITE 600 WASHINGTON, DC 20004				
EXAMINER				
HOBBS, LISA JOE				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/586,329

Applicant(s)

EBNETH ET AL.

Examiner

Lisa J. Hobbs

Art Unit

1657

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 July 2006 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SI.08)
Paper No(s)/Mail Date 11/2009
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Priority

The provisional application from which the instant application claims priority was filed in a language other than English. An English translation of a non-English provisional application must be filed in either the provisional application or in each nonprovisional application that claims the benefit of the provisional application filing date under 35 USC 119(e). Therefore, if an English translation and a statement that the translation is accurate have not been filed in the above-identified provisional application when a nonprovisional application is filed claiming the benefit of the filing date of the provisional application, the Office will mail a Notice requiring an English translation and the statement in each later-filed nonprovisional application claiming priority to the above-identified provisional application.

In the event that the Office schedules a nonprovisional application that claims the benefit of a provisional application filed in a language other than English for publication without issuing a Notice requiring the applicant to file an English translation of the non-English provisional application, the applicant should file the English translation of the non-English provisional application and a statement that the translation is accurate before the scheduled publication date. 37 CFR 1.78(a)(5) states in part:

(iv) If the prior-filed provisional application was filed in a language other than English and an English- language translation of the prior-filed provisional application and a statement that file translation is accurate were not previously filed in the prior-filed provisional application or the later-filed nonprovisional application, applicant will be notified and given a period of time within which to file an English language translation of

the non-English-language prior-filed provisional application and a statement that the translation is accurate. In a pending nonprovisional application, failure to timely reply to such a notice will result in abandonment of the application.

Information Disclosure Statement

The information disclosure statement(s) (IDS) submitted on 30 November 2009 is/are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

The drawings are objected to because Figure 7 has two panels but they are not labelled panels A and B to clearly delineate them when referenced in the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR

1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The specification must contain a Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f), which is a reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74. The specification is apparently missing this section and must be updated to appropriately describe the figures submitted 14 July 2006. Please note the objection to the drawings, i.e., that there must be a description of panels A and B for Figure 7.

Claim Status

Claims 1-31 are active in the case. No claims have been cancelled by preliminary amendment. Claims 1-31 are under examination; no claims are withdrawn as drawn to a non-elected invention.

Claim Objections

37 CFR 1.121 provides the proper form for submitting changes to claims, it states (in part):

(c) Claims. Amendments to a claim must be made by rewriting the entire claim with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled.

Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).

(1) Claim listing. All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of “canceled” or “not entered” may be aggregated into one statement (e.g., Claims 1 – 5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.

(2) When claim text with markings is required. All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of “currently amended,” and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of “currently amended,” or “withdrawn” if also being amended, shall

include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as “withdrawn— currently amended.”

(3) When claim text in clean version is required. The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, i.e., without any markings in the presentation of text. The presentation of a clean version of any claim having the status of “original,” “withdrawn” or “previously presented” will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of “withdrawn” or “previously presented.” Any claim added by amendment must be indicated with the status of “new” and presented in clean version, i.e., without any underlining.

(4) When claim text shall not be presented; canceling a claim.

(i) No claim text shall be presented for any claim in the claim listing with the status of “canceled” or “not entered.”

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as “canceled” will constitute an instruction to cancel the claim.

(5) Reinstatement of previously canceled claim. A claim which was previously canceled may be reinstated only by adding the claim as a “new” claim with a new claim number.

Claims 1 and 2 are objected to because of the following informalities: A comparison of the original claim set with the claims from “Amendment A” submitted 14 July 2006 and then with “Amendment B” submitted 05 October 2009 shows that although claims 1 and 2 are both designated as “Original” there has been a deletion of the less than or equal to sign in each of the

claims. This also apparently removes some of the support for later temperature ranges in dependent claims. A new claim set with all claim changes marked, the entire claim set has not been combed for any other discrepancies between the earlier submitted claims and the current claim set, as required and each claim appropriately designated as "Original", "Amended", etc., is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors. After a careful comparison between the instant claims and the claims of the parent provisional case (60/536514), along with the amendments that have been made since the filing of the instant case, which are mostly to correct multiple dependencies, it appears that the claims under examination are substantially literal translations of the original German claims. For example, the measuring parameter "being a membrane potential", that a "sample" is "provid[ed]" (which word does not make clear if the sample is live tissue such as from surgery as noted in the IPER, or is in vitro membrane or tissue comprising ion channels, or is a sample of ion channels completely purified, e.g., removed from all

membrane in some way, and the word “provided” is the literal translation of the word “bereitstellen” from the parent case), that various activities are “examined” (without recitation of how they would be examined, e.g., a positive method step), that some methods are “for use in research” or that the methods are practiced “using” various compounds (again without any recitation of how they would be used) . Finally, the claims consistently use the phrase “characterised in that” where usual practice recites the term “wherein”. Claim 1 also recites that samples will be characterized by determining values of some parameters and recites a specific temperature limitation, however there also appears from the examples to be a specific limitation needed in the claim requiring the use of inhibitors, blockers, or other activity modulators of the various ion channels, in addition to the temperature requirement, which is not part of the instant method narrative.

There are numerous instances where the use of non-standard phrasing has created claims that are indefinite, not providing a clear delineation of the metes and bounds of the claims. For example, these phrases could have multiple interpretations: that the method is for “examining the activity of ion channels” from claim 1, that one step is “determining a value of a measuring parameter” from claim 1 as well. Also, in one claim a dye “serves as a measure” of an ion channel characteristic and in another claim a concentration of an element “is determined as an indicator” of activity and it is unclear if these phrases are intended to impart the same characteristics to the products or not. Claims 10, 11, and 12 all recite that a particular channel activity “is examined” but it is not clear exactly how this is to be accomplished as there are no specific method steps elucidated. Claim 1 comprises a list of values one might determine or measure, but the list is not specific, for example the differences between “ion concentration” and

“a measure of ion concentration” is not clear. It is suggested that the claims use a consistent “active voice” and move away from constructions using passive voice and indirect activity.

As well, the claims contain multiple instances of language where ranges, not in any variants of accepted Markush language, are claimed. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by “such as” and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Some examples of claims that have a concomitant recitation of broad and limited ranges are: the temperatures ranges of claims 2 and 3; the use of the phrases “in particular” in claims 4, 6, 13, 18, 21, 22, 23, 24 and 25; “preferably” in claims 14 and 22; and the recitation of “especially” in claims 15, 16, 18 and 19. As well, claim 17 recites the limitation “the values of several measuring parameters”, while claim 1 recites that one measuring parameter is used. Claims 2 and 3 fail to further limit the “about 10” degrees from claim 1, thus there is insufficient antecedent basis for this limitation in the claim.

For the purposes of this examination, the examiner is interpreting the independent claim to be drawn to a method for measuring the activity of ion channels in an in vitro environment via measurement of changes in membrane potential or ion concentration using fluorescence, radioactive or atomic absorption methods, wherein the measurements are performed at a temperature of 10 °C or below, as in claims 2 and 3, with subsequent claims delineating specific tissues, organelles, and methods of measurement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siem-Fung et al. ((1983) *Biochim et Biophys Acta* 728(3): 305-10), Weaver (US 2002/0168625 A), Kim et al. ((2000) *Am. J. Phys. Reg. Int. Comp. Physiol.* 278(6): R1524-R1534), Mitsuiye et al. ((1997) *Japanese J. Physiol.* 47(1): 73-79), Chung et al. ((1995) *Neurosci. Lett.* 187(3): 181-4), Ding ((1993) *Plant J. Cell Mol. Biol.* 3(5): 713-20), in view of Netzer et al ((2001) *Drug Discovery Today* 6(2): 78-84) and Numann et al. ((2001) *Trends in Cardiovasc. Med.* 11(2): 54-9).

The examiner is interpreting the independent claim to be drawn to a method for measuring the activity of ion channels in an in vitro environment via measurement of changes in membrane potential or ion concentration using fluorescence, radioactive or atomic absorption methods, wherein the measurements are performed at a temperature of 10 °C or below, as in claims 2 and 3, with subsequent claims delineating specific tissues, organelles, and methods of measurement.

Siem-Fung et al. teach a method comprising determining the effects of veratridine on ion channel activity in squid axons, by measuring the cell membrane potential and ion (potassium and sodium) concentration in the squid axons, wherein the method is carried out at 5°C (Fig. 1 and Tables 1 and 2).

Weaver et al. teach "[a] method for identifying a modulator of an ion channel, channel-linked receptor or ion transporter comprising: (a) contacting cells expressing ion channels, ion channels and channel-linked receptors, or ion transporters with a signal-generating thallium

sensitive agent; (b) contacting said cells with a candidate modulator; (c) contacting the cells with an assay buffer containing a thallium salt solution; and (d) detecting and measuring the signal generated by the signal generating thallium sensitive agent, wherein the signal generated by the signal generating thallium sensitive agent is an indication of the effect of the modulator on the activity of said ion channels, channel-linked receptors, or ion transporters. The method further comprising the step of measuring the signal generated by the signal generating thallium sensitive agent after step (b), and wherein said modulator activates or inhibits said ion channels, channel-linked receptors, or ion transporters" (claims 27-29).

Kim et al. teach a method of determining the effects of forskolin and Bay K8644 on voltage-gated calcium ion channel activity in ventricular cells by measuring the cell membrane potential, wherein the said method is carried out at 4 °C (Figs. 9-10, Tables 1 and 2).

Mitsuiye et al. teach a method of measuring the activity of voltage-sensitive potassium channels of cardiac myocytes, wherein the membrane potential is determined at 5 °C (Fig. 1).

Chung et al. teach a method of measuring the activity of transmitter-dependent ion channels of hippocampal cells, wherein the membrane potential is determined at 5 °C (Fig. 1).

Ding et al. teach a method of measuring the activity of mechano-sensitive calcium channels of onion epidermal cells, wherein the ion channel currents are determined at 1-5 °C (p. 713, col. 2, Fig. 1).

Netzer et al. teach that fluorometric assays are used in various HTS methodologies, in particular, in assays of ion channels, in which the properties of potentiometric fluorescent dyes are exploited, wherein upon alteration of cell membrane potential, either alterations in

fluorescent intensity occur or the dyes perform fluorescence energy resonance transfer (FRET) with dyes outside the membrane (see, for example, page 82).

Numann et al. teach that a variety of optical technologies are available for detecting ion channel activity in living cells; they teach that fluorescent Ca^{2+} indicator dyes allow for screening of calcium channels and compounds which trigger intracellular Ca^{2+} release. Further, Numann et al teach that these dyes can be assayed using multi-well microtiter plates using specialized kinetic plate readers and that indicators of membrane potential can be used and are extremely sensitive because relatively small currents can cause large voltage changes. They also teach that a commonly used optical method for measurement of membrane potential is based on fluorescent oxonol dye, which utilizes FRET (p. 56-57).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods disclosed in the articles detailing that one of skill would be aware of a variety of ion channel types, cell types, parameters for measurement, measurement methods, and that the use of low temperatures for the measurements is known. Netzer et al. and Numann et al. teach the use of art-recognized equivalent methods of measuring membrane potentials or ion concentrations in place of conventional patch clamping, as discussed above. Therefore, based upon the combination of teachings, it would have been both obvious and beneficial for one of ordinary skill in the art to substitute fluorescent, or other methods, methods for those taught by the various skilled artisans. The result-effective adjustment of particular conventional working conditions (e.g., using a particular method of measuring ion channel activity and/or membrane potential) is deemed merely a matter of judicious selection

and routine optimization which is well within the purview of one of skill in the art of ion channel measurement.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Hobbs whose telephone number is 571-272-3373. The examiner can normally be reached on Hotelling - Generally, 9-6 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lisa J. Hobbs/
Primary Examiner
Art Unit 1657